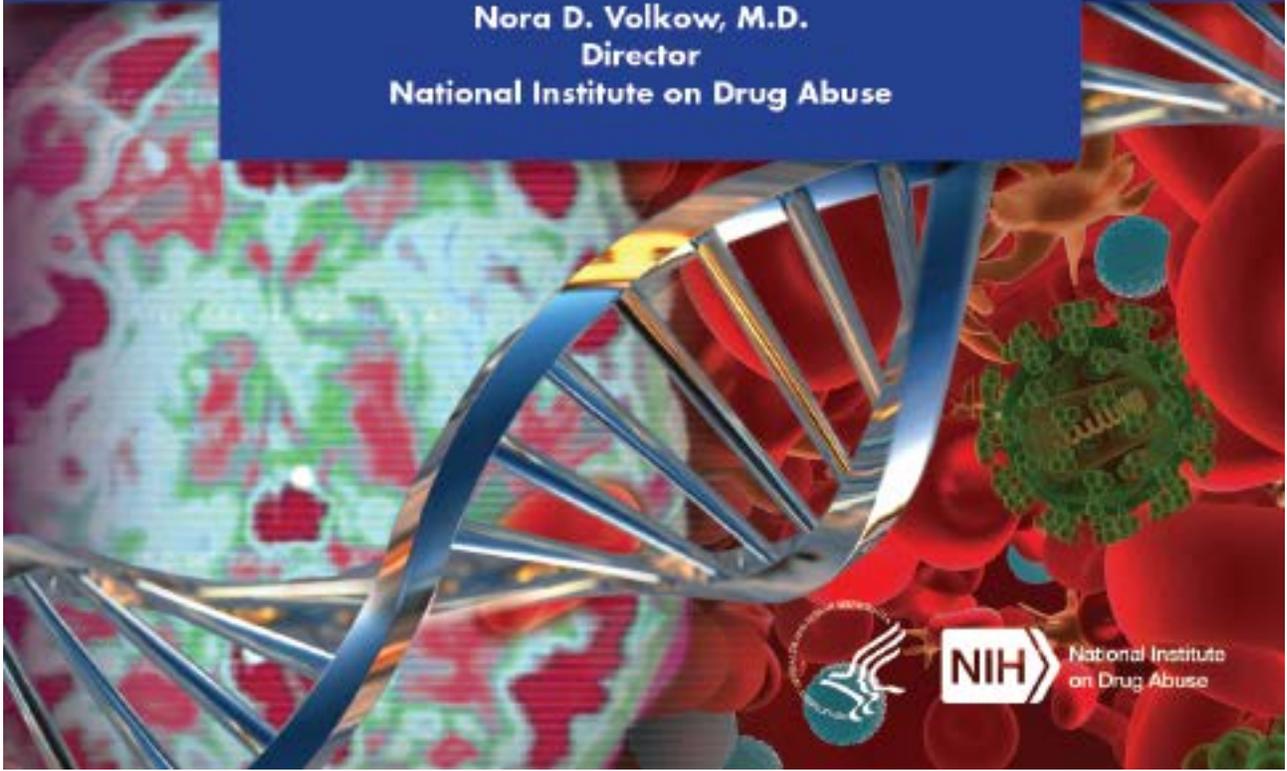




DIRECTOR'S REPORT

to the
National Advisory Council on Drug Abuse
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Director
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National Institute
on Drug Abuse

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RESEARCH HIGHLIGHTS

BASIC AND BEHAVIORAL RESEARCH

Reversal And Prevention Of The Respiratory-Depressant Effects Of Heroin By The Novel M-Opioid Receptor Antagonist Methocinnamox In Rhesus Monkeys

Gerak LR, Maguire DR, Woods JH, Husbands SM, Disney A, France CP. *J Pharmacol Exp Ther.* 2019; 368: 229-236. One consequence of the ongoing opioid epidemic is a large number of overdose deaths. Naloxone reverses opioid-induced respiratory depression; however, its short duration of action limits the protection it can provide. Methocinnamox (MCAM) is a novel opioid receptor antagonist with a long duration of action. This study examined the ability of MCAM to prevent and reverse the respiratory-depressant effects (minute volume [V_E]) of heroin in five monkeys. MCAM (0.32 mg/kg) was given before heroin to determine whether it prevents respiratory depression; heroin dose-effect curves were generated 1, 2, 4, and 8 days later, and these effects were compared with those of naltrexone (0.032 mg/kg). Heroin dose dependently decreased V_E . MCAM and naltrexone prevented respiratory depression, shifting the heroin dose-effect curve rightward at least 10-fold. MCAM, but not naltrexone, attenuated these effects of heroin for 4 days. MCAM (0.1-0.32 mg/kg) was given 30 minutes after heroin to determine whether it reverses respiratory depression; heroin dose-effect curves were generated 1, 2, 4, 8, and 16 days later, and these effects were compared with those of naloxone (0.0032-0.1 mg/kg). MCAM and naloxone reversed respiratory depression within 30 minutes, although only MCAM antagonized heroin on subsequent days. Thus, MCAM prevents and reverses respiratory depression, the potentially lethal effect of heroin, longer than opioid receptor antagonists currently in use. Because of its sustained effects, MCAM might provide more effective rescue from and protection against the fatal respiratory-depressant effects of opioids, thereby improving treatment of opioid overdose.

Determining The Pharmacokinetics Of Nicotinic Drugs In The Endoplasmic Reticulum Using Biosensors

Shivange AV, Borden PM, Muthusamy AK, Nichols AL, Bera K, Bao H, Bishara I, Jeon J, Mulcahy MJ, Cohen B, O'Riordan SL, Kim C, Dougherty DA, Chapman ER, Marvin JS, Looger LL, Lester HA. *J Gen Physiol.* 2019 Feb 4. [Epub ahead of print]. Nicotine dependence is thought to arise in part because nicotine permeates into the endoplasmic reticulum (ER), where it binds to nicotinic receptors (nAChRs) and begins an "inside-out" pathway that leads to up-regulation of nAChRs on the plasma membrane. However, the dynamics of nicotine entry into the ER are unquantified. Here, the authors developed a family of genetically encoded fluorescent biosensors for nicotine, termed iNicSnFRs. The iNicSnFRs are fusions between two proteins: a circularly permuted GFP and a periplasmic choline-/betaine-binding protein engineered to bind nicotine. The biosensors iNicSnFR3a and iNicSnFR3b respond to nicotine by increasing fluorescence at [nicotine] $<1 \mu\text{M}$, the concentration in the plasma and cerebrospinal fluid of a smoker. The authors target iNicSnFR3 biosensors either to the plasma membrane or to the ER and measure nicotine kinetics in HeLa, SH-SY5Y, N2a, and HEK293 cell lines, as well as mouse hippocampal neurons and human stem cell-derived dopaminergic neurons. In all cell types, they found that nicotine equilibrates in the ER within 10 s (possibly within 1 s) of extracellular application and leaves as rapidly after removal from the extracellular solution. The [nicotine] in the ER is within twofold of the extracellular value. The authors use these data to run combined pharmacokinetic and pharmacodynamic simulations of human smoking. In the ER, the inside-out pathway begins when nicotine becomes a stabilizing pharmacological chaperone for some nAChR subtypes, even at concentrations as low as $\sim 10 \text{ nM}$. Such concentrations would persist during the

12 h of a typical smoker's day, continually activating the inside-out pathway by >75%. Reducing nicotine intake by 10-fold decreases activation to ~20%. iNicSnFR3a and iNicSnFR3b also sense the smoking cessation drug varenicline, revealing that varenicline also permeates into the ER within seconds. The authors' iNicSnFRs enable optical subcellular pharmacokinetics for nicotine and varenicline during an early event in the inside-out pathway.

The Delta Opioid Receptor Positive Allosteric Modulator BMS 986187 Is A G-Protein-Biased Allosteric Agonist

Stanczyk MA, Livingston KE, Chang L, Weinberg ZY, Puthenveedu M, Traynor JR. Br. J. Pharmacol. 2019 Feb 2. [Epub ahead of print].

BACKGROUND AND PURPOSE: The δ -opioid receptor is an emerging target for the management of chronic pain and depression. Biased signaling, the preferential activation of one signaling pathway over another downstream of δ -receptors, may generate better therapeutic profiles. BMS 986187 is a positive allosteric modulator of δ -receptors. Here, the authors ask if BMS 986187 can directly activate the receptor from an allosteric site, without an orthosteric ligand, and if a signaling bias is generated.

EXPERIMENTAL APPROACH: We used several clonal cell lines expressing δ -receptors, to assess effects of BMS 986187 on events downstream of δ -receptors by measuring G-protein activation, β -arrestin 2 recruitment, receptor phosphorylation, loss of surface receptor expression, ERK1/ERK2 phosphorylation, and receptor desensitization.

KEY RESULTS: BMS 986187 is a G protein biased allosteric agonist, relative to β -arrestin 2 recruitment. Despite showing direct and potent G protein activation, BMS 986187 has a low potency to recruit β -arrestin 2. This appears to reflect the inability of BMS 986187 to elicit any significant receptor phosphorylation, consistent with low receptor internalization and a slower onset of desensitization, compared with the full agonist SNC80.

CONCLUSIONS AND IMPLICATIONS: This is the first evidence of biased agonism mediated through direct binding to an allosteric site on an opioid receptor, without a ligand at the orthosteric site. These data suggest that agonists targeting δ -receptors, or indeed any GPCR, through allosteric sites may be a novel way to promote signaling bias and thereby potentially produce a more specific pharmacology than can be observed by activation via the orthosteric site.

Pain-Induced Negative Affect Is Mediated via Recruitment of the Nucleus Accumbens Kappa Opioid System

Massaly N, Copits BA, Wilson-Poe AR, Hipólito L, Markovic T, Yoon HJ, Liu S, Walicki MC, Bhatti DL, Sirohi S, Klaas A, Walker BM, Neve R, Cahill CM, Shoghi KI, Gereau RW 4th, McCall JG, Al-Hasani R, Bruchas MR, Morón JA. Neuron. 2019 Mar 4. [Epub ahead of print].

Negative affective states affect quality of life for patients suffering from pain. These maladaptive emotional states can lead to involuntary opioid overdose and many neuropsychiatric comorbidities. Uncovering the mechanisms responsible for pain-induced negative affect is critical in addressing these comorbid outcomes. The nucleus accumbens (NAc) shell, which integrates the aversive and rewarding valence of stimuli, exhibits plastic adaptations in the presence of pain. In discrete regions of the NAc, activation of the kappa opioid receptor (KOR) decreases the reinforcing properties of rewards and induces aversive behaviors. Using complementary techniques, the authors report that in vivo recruitment of NAc shell dynorphin neurons, acting through KOR, is necessary and sufficient to drive pain-induced negative affect. Taken together, these results provide evidence that pain-induced adaptations in the kappa opioid system within the NAc shell represent a functional target for therapeutic intervention that could circumvent pain-induced affective disorders.

Histone Serotonylation Is A Permissive Modification That Enhances TFIID Binding To H3K4me3

Farrelly LA, Thompson, RE, Zhao, S, Lepack AE, Lyu Y, Bhanu NV, Zhang B, Loh YE, Ramakrishnan A, Vadodaria KC, Heard KJ, Erikson G, Nakadai T, Bastle RM, Lukasak BJ, Zebroski H 3rd, Alenina N, Bader M, Berton O, Roeder RG, Molina H, Gage FH, Shen L, Garcia BA, Li H, Muir TW, Maze I. *Nature*. 2019 Mar; 567(7749): 535-539.

Chemical modifications of histones can mediate diverse DNA-templated processes, including gene transcription. Here the authors provide evidence for a class of histone post-translational modification, serotonylation of glutamine, which occurs at position 5 (Q5ser) on histone H3 in organisms that produce serotonin (also known as 5-hydroxytryptamine (5-HT)). They demonstrate that tissue transglutaminase 2 can serotonylate histone H3 tri-methylated lysine 4 (H3K4me3)-marked nucleosomes, resulting in the presence of combinatorial H3K4me3Q5ser *in vivo*. H3K4me3Q5ser displays a ubiquitous pattern of tissue expression in mammals, with enrichment observed in brain and gut, two organ systems responsible for the bulk of 5-HT production. Genome-wide analyses of human serotonergic neurons, developing mouse brain and cultured serotonergic cells indicate that H3K4me3Q5ser nucleosomes are enriched in euchromatin, are sensitive to cellular differentiation and correlate with permissive gene expression, phenomena that are linked to the potentiation of TFIID interactions with H3K4me3. Cells that ectopically express a H3 mutant that cannot be serotonylated display significantly altered expression of H3K4me3Q5ser-target loci, which leads to deficits in differentiation. Taken together, these data identify a direct role for 5-HT, independent from its contributions to neurotransmission and cellular signaling, in the mediation of permissive gene expression.

EPIDEMIOLOGY, PREVENTION, AND SERVICES RESEARCH

Assessment Of Exposure To High-Performing Schools And Risk Of Adolescent Substance Use: A Natural Experiment

Dudovitz RN, Chung PJ, Reber S, Kennedy D, Tucker JS, Shoptaw S, Dosanjh KK, Wong MD. *JAMA Pediatr*. 2018 Dec 1; 172(12): 1135-1144.

Importance: Although school environments are thought to influence health behaviors, experimental data assessing causality are lacking, and which aspects of school environments may be most important for adolescent health are unknown.

Objective: To test whether exposure to high-performing schools is associated with risky adolescent health behaviors.

Design, Setting, and Participants: This natural experiment used admission lotteries, which mimic random assignment, to estimate the association of school environments and adolescent health. A survey of 1270 students who applied to at least 1 of 5 high-performing public charter schools in low-income minority communities in Los Angeles, California. Schools had an academic performance ranked in the top tertile of Los Angeles County public high schools, applicants outnumbered available seats by at least 50, and an admissions lottery was used. Participants included lottery winners (intervention group [n = 694]) and lottery losers (control group [n = 576]) from the end of 8th grade and beginning of 9th grade through the end of 11th grade. Intention-to-treat (ITT) and instrumental variable techniques estimated the association of winning the lottery and attending high-performing schools with health behaviors and whether the association varied by sex. Data were collected from March 11, 2013, through February 22, 2017, and analyzed from October 1, 2017, through July 1, 2018.

Exposures: Schools were considered high performing if they placed in the top tertile of public high schools in LA County on 2012 state standardized tests. Most students attended that same school for 3 years (9th-11th grades).

Main Outcomes and Measures: Primary self-reported outcomes were 30-day and high-risk self-reported marijuana use. Additional health outcomes included 30-day alcohol use, alcohol misuse, ever being in a fight, ever having sex, and past-year delinquency. Potential intermediate factors (time studying, truancy, school mobility, school culture, school order, teacher support for college, and proportion of substance-using peers in students' social networks) were also examined.

Results: Among the 1270 participating students (52.6% female; mean [SD] age at enrollment, 14.3 [0.5] years), ITT analysis showed that the intervention group reported less marijuana misuse than the control group (mean marijuana misuse score, 0.46 vs 0.71), as well as fewer substance-using peers (9.6% vs 12.7%), more time studying (mean, 2.63 vs 2.49 hours), less truancy (84.3% vs 77.3% with no truancy), greater teacher support for college (mean scores, 7.20 vs 7.02), more orderly schools (mean order score, 7.06 vs 6.83), and less school mobility (21.4% vs 28.4%) (all $P < .05$). Stratified analyses suggest that among boys, intervention participants had significantly lower marijuana use (mean misuse score, 0.43 vs 0.88; difference, -0.45; 95% CI, -0.78 to -0.13) and alcohol misuse (mean misuse score, 0.52 vs 0.97; difference, -0.44; 95% CI, -0.80 to -0.09) scores compared with control participants, whereas no significant health outcomes were noted for girls.

Conclusions and Relevance: This natural experiment provides evidence that school environments can improve risky behaviors for low-income minority adolescents.

[Methadone Maintenance Treatment Among Patients Exposed To Illicit Fentanyl In Rhode Island: Safety, Dose, Retention, And Relapse At 6 Months](#) Stone AC, Carroll JJ, Rich JD, Green TC. *Drug Alcohol Depend.* 2018; 192: 94-97.

INTRODUCTION: Illicitly manufactured fentanyl (IMF) is a potent synthetic opioid that has been contributing to overdose deaths in the United States. This study examined intake toxicology and six-month treatment outcomes for patients newly admitted to a single methadone maintenance treatment program (MMTP) in Rhode Island with a high prevalence of illicit fentanyl.

METHODS: We conducted a retrospective chart review of patients admitted to a single MMTP between November 1st, 2016 and August 31st, 2017 followed for six months. Outcomes measured included: 1) retention in treatment at 6 months; 2) evidence of sustained abstinence; 3) relapse; 4) methadone dosage required to achieve sustained abstinence; and 5) the number of days required to achieve abstinence.

RESULTS: We observed 154 unique intake events (representing 147 patients). 80% ($n = 123$) tested positive for fentanyl at intake. During the six-month follow up period, 32% ($n = 49$) left treatment before six months, two individuals died within five weeks of discontinuation. No deaths were seen among those remaining in treatment. The majority (89%) who remained in treatment at six months achieved abstinence. No significant difference was seen for dose or time to achieve abstinence. Relapse was common (57%). Repeated exposure to fentanyl was seen frequently (71%) while in MMT before and after achieving abstinence.

CONCLUSION: While there is concern that the potency of IMF may reduce the effectiveness of MAT, this study suggests that MMT is safe, abstinence achievable, and MMT is protective against death among fentanyl-exposed patients.

[Genetic Predisposition Vs Individual-Specific Processes In The Association Between Psychotic-Like Experiences And Cannabis Use](#) Karcher NR, Barch DM, Demers CH, Baranger DA, Heath AC, Lynskey MT, Agrawal A. *JAMA Psychiatry.* 2019; 76(1): 87-94.

IMPORTANCE: Previous research indicates that cannabis use is associated with psychotic-like experiences (PLEs). However, it is unclear whether this association results from predispositional

(ie, shared genetic) factors or individual-specific factors (eg, causal processes, such as cannabis use leading to PLEs).

OBJECTIVES: To estimate genetic and environmental correlations between cannabis use and PLEs, and to examine PLEs in twin and nontwin sibling pairs discordant for exposure to cannabis use to disentangle predispositional from individual-specific effects.

DESIGN, SETTING, AND PARTICIPANTS: In this cross-sectional analysis, diagnostic interviews and self-reported data were collected from 2 separate population-based samples of twin and nontwin sibling pairs. Data from the Human Connectome Project were collected between August 10, 2012, and September 29, 2015, and data from the Australian Twin Registry Cohort 3 (ATR3) were collected between August 1, 2005, and August 31, 2010. Data were analyzed between August 17, 2017, and July 6, 2018. The study included data from 1188 Human Connectome Project participants and 3486 ATR3 participants, totaling 4674 participants.

MAIN OUTCOMES AND MEASURES: Three cannabis-involvement variables were examined: frequent use (ie, ≥ 100 times), a DSM-IV lifetime cannabis use disorder diagnosis, and current cannabis use. Genetic and environmental correlations between cannabis involvement and PLEs were estimated. Generalized linear mixed models examined PLE differences in twin and nontwin sibling pairs discordant for cannabis use.

RESULTS: Among the 4674 participants, the mean (SD) age was 30.5 (3.2) years, and 2923 (62.5%) were female. Data on race/ethnicity were not included as a covariate owing to lack of variability within the ATR3 sample; among the 1188 participants in the Human Connectome Project, 875 (73.7%) were white. Psychotic-like experiences were associated with frequent cannabis use ($\beta = 0.11$; 95% CI, 0.08-0.14), cannabis use disorder ($\beta = 0.13$; 95% CI, 0.09-0.16), and current cannabis use ($\beta = 0.07$; 95% CI, 0.04-0.10) even after adjustment for covariates. Correlated genetic factors explained between 69.2% and 84.1% of this observed association. Within discordant pairs of twins/siblings (Npairs, 308-324), Psychotic-like experiences were more common in cannabis-exposed individuals compared with their relative who used cannabis to a lesser degree ($\beta \geq .23$, $P < .05$; eg, frequent and infrequent cannabis-using relatives significantly differed, $z = -5.41$; $P < .001$).

CONCLUSIONS AND RELEVANCE: Despite the strong contribution of shared genetic factors, frequent and problem cannabis use also appears to be associated with PLEs via person-specific pathways. This study's findings suggest that policy discussions surrounding legalization should consider the influence of escalations in cannabis use on traitlike indices of vulnerability, such as PLEs, which could contribute to pervasive psychological and interpersonal burden.

[Addressing The Nexus Of Risk: Biobehavioral Outcomes From A Cluster Randomized Trial Of The Women's Health CoOp Plus In Pretoria, South Africa](#) Wechsberg WM, Bonner CP, Zule WA, van der Horst C, Ndirangu J, Browne FA, Kline TL, Howard BN, Rodman NF. Drug Alcohol Depend. 2019; 195: 16-26.

BACKGROUND: HIV prevalence has increased among South African women who use alcohol and other drugs (AOD). However, HIV prevention and treatment efforts have not focused on this population. This study presents the efficacy of the Women's Health CoOp Plus (WHC+) in a cluster-randomized trial to reduce AOD use, gender-based violence, and sexual risk and to increase linkage to HIV care among women who use AODs, compared with HIV counseling and testing alone.

METHODS: Black African women (N = 641) were recruited from 14 geographic clusters in Pretoria, South Africa, and underwent either an evidence-based gender-focused HIV prevention intervention that included HIV counseling and testing (WHC+) or HIV counseling and testing alone. Participants were assessed at baseline, 6-months, and 12-months post enrollment.

RESULTS: At 6-month follow-up, the WHC+ arm (vs. HCT) reported more condom use with a main partner and sexual negotiation, less physical and sexual abuse by a boyfriend, and less frequent heavy drinking ($p < 0.05$). At 12-month follow-up, the WHC+ arm reported less emotional abuse ($p < 0.05$). Among a subsample of women, the WHC+ arm was significantly more likely to have a non-detectable viral load (measured by dried blood spots; $p = 0.01$).

CONCLUSION: The findings demonstrate the WHC+'s efficacy to reduce HIV risk among women who use AODs in South Africa. Substance abuse rehabilitation centers and health centers that serve women may be ideal settings to address issues of gender-based violence and sexual risk as women engage in substance use treatment, HIV testing, or HIV care.

Receipt Of Timely Addiction Treatment And Association Of Early Medication Treatment With Retention In Care Among Youths With Opioid Use Disorder

Hadland SE, Bagley SM, Rodean J, Silverstein M, Levy S, Laroche MR, Samet JH, Zima BT. JAMA Pediatr. 2018; 172(11): 1029-1037.

IMPORTANCE: Retention in addiction treatment is associated with reduced mortality for individuals with opioid use disorder (OUD). Although clinical trials support use of OUD medications among youths (adolescents and young adults), data on timely receipt of buprenorphine hydrochloride, naltrexone hydrochloride, and methadone hydrochloride and its association with retention in care in real-world treatment settings are lacking.

OBJECTIVES: To identify the proportion of youths who received treatment for addiction after diagnosis and to determine whether timely receipt of OUD medications is associated with retention in care.

DESIGN, SETTING, AND PARTICIPANTS: This retrospective cohort study used enrollment data and complete health insurance claims of 2.4 million youths aged 13 to 22 years from 11 states enrolled in Medicaid from January 1, 2014, to December 31, 2015. Data analysis was performed from August 1, 2017, to March 15, 2018.

EXPOSURES: Receipt of OUD medication (buprenorphine, naltrexone, or methadone) within 3 months of diagnosis of OUD compared with receipt of behavioral health services alone.

MAIN OUTCOMES AND MEASURES: Retention in care, with attrition defined as 60 days or more without any treatment-related claims.

RESULTS: Among 4837 youths diagnosed with OUD, 2752 (56.9%) were female and 3677 (76.0%) were non-Hispanic white. Median age was 20 years (interquartile range [IQR], 19-21 years). Overall, 3654 youths (75.5%) received any treatment within 3 months of diagnosis of OUD. Most youths received only behavioral health services (2515 [52.0%]), with fewer receiving OUD medications (1139 [23.5%]). Only 34 of 728 adolescents younger than 18 years (4.7%; 95% CI, 3.1%-6.2%) and 1105 of 4109 young adults age 18 years or older (26.9%; 95% CI, 25.5%-28.2%) received timely OUD medications. Median retention in care among youths who received timely buprenorphine was 123 days (IQR, 33-434 days); naltrexone, 150 days (IQR, 50-670 days); and methadone, 324 days (IQR, 115-670 days) compared with 67 days (IQR, 14-206 days) among youths who received only behavioral health services. Timely receipt of buprenorphine (adjusted hazard ratio, 0.58; 95% CI, 0.52-0.64), naltrexone (adjusted hazard ratio, 0.54; 95% CI, 0.43-0.69), and methadone (adjusted hazard ratio, 0.32; 95% CI, 0.22-0.47) were each independently associated with lower attrition from treatment compared with receipt of behavioral health services alone.

CONCLUSIONS AND RELEVANCE: Timely receipt of buprenorphine, naltrexone, or methadone was associated with greater retention in care among youths with OUD compared with behavioral treatment only. Strategies to address the underuse of evidence-based medications for youths with OUD are urgently needed.

TREATMENT RESEARCH

[Comparison Of The Pharmacokinetic Properties Of Naloxone Following The Use Of FDA-Approved Intranasal And Intramuscular Devices Versus A Common Improvised Nasal Naloxone Device](#) Krieter PA, Chiang CN, Gyaw S, McCann DJ. J Clin Pharmacol. 2019 Mar 12. [E-pub ahead of print].

For more than a decade, first responders and the general public have been able to treat suspected opioid overdoses using an improvised nasal naloxone device (INND) constructed from a prefilled syringe containing 2 mg of naloxone (1 mg/mL) attached to a mucosal atomization device. In recent years, the U.S. Food and Drug Administration (FDA)-approved Ezvio, an autoinjector that delivers 2 mg by intramuscular injection and Narcan nasal spray (2- and 4-mg strengths; 0.1 mL/dose) for the emergency treatment of a known or suspected opioid overdose. The present study was conducted to compare the pharmacokinetics of naloxone using the FDA-approved devices (each administered once) and either 1 or 2 administrations using the INND. When naloxone was administered twice using the improvised device, the doses were separated by 2 minutes. The highest maximum plasma concentration was achieved using the 4-mg FDA-approved spray. The highest exposures at 5 minutes postdose, based on AUC values, were after administration with the autoinjector and the 4-mg FDA-approved spray; at 10, 15, and 20 minutes postdose, the latter yielded the greatest exposure. Even after 2 administrations, the INND failed to achieve naloxone plasma levels comparable to the FDA-approved devices at any time. The ease of use and higher plasma concentrations achieved using the 4-mg FDA-approved spray, compared with the INND, should be considered when deciding which naloxone device to use.

[Fighting Fire With Fire: Development Of Intranasal Nalmefene To Treat Synthetic Opioid Overdose](#) Krieter P, Gyaw S, Crystal R, Skolnick P. J Pharmacol Exp Ther. 2019 Apr 2. pii: jpet.118.256115. [Epub ahead of print].

The dramatic rise in overdose deaths linked to synthetic opioids (e.g., fentanyl, carfentanil) may require more potent, longer duration opiate antagonists than naloxone. Both the high affinity of nalmefene at μ opiate receptors and its long half-life led us to examine the feasibility of developing an intranasal (IN) formulation as a rescue medication that could be especially useful in treating synthetic opioid overdose. In this study, the pharmacokinetic properties of IN nalmefene were compared with an intramuscular (IM) injection in a cohort of healthy volunteers. Nalmefene was absorbed slowly following IN administration, with a median T_{max} of 2 h. Addition of the absorption enhancer dodecyl maltoside (Intravail®) reduced T_{max} to 0.25 h and increased C_{max} by ~2.2-fold. The pharmacokinetic properties of IN nalmefene (3 mg) formulated with dodecyl maltose has characteristics consistent with an effective rescue medication: its onset of action is comparable to an IM injection of nalmefene (1.5 mg) previously approved to treat opioid overdose. Furthermore, the C_{max} following IN administration is ~3-fold higher than following IM dosing, comparable to previously reported plasma concentrations of nalmefene observed 5 min. following a 1 mg IV dose. The high affinity, very rapid onset, and long half-life (>7 h) of IN nalmefene present distinct advantages as a rescue medication, particularly against longer-lived synthetic opioids.

[A Fentanyl Vaccine Alters Fentanyl Distribution And Protects Against Fentanyl-Induced Effects In Mice And Rats](#) Raleigh MD, Baruffaldi F, Peterson SJ, Le Naour M, Harmon TM, Vigliaturo JR, Pentel PR, Pravetoni M. J Pharmacol Exp Ther. 2019; 368(2): 282-291.

Fentanyl is an extremely potent synthetic opioid that has been increasingly used to adulterate heroin, cocaine, and counterfeit prescription pills, leading to an increase in opioid-induced fatal overdoses in the United States, Canada, and Europe. A vaccine targeting fentanyl could offer protection against the toxic effects of fentanyl in both recreational drug users and others in professions at risk of accidental exposure. This study focuses on the development of a vaccine consisting of a fentanyl-based hapten (F) conjugated to keyhole limpet hemocyanin (KLH) carrier protein or to GMP-grade subunit KLH (sKLH). Immunization with F-KLH in mice and rats reduced fentanyl-induced hotplate antinociception, and in rats reduced fentanyl distribution to the brain compared with controls. F-KLH did not reduce the antinociceptive effects of equianalgesic doses of heroin or oxycodone in rats. To assess the vaccine effect on fentanyl toxicity, rats immunized with F-sKLH or unconjugated sKLH were exposed to increasing subcutaneous doses of fentanyl. Vaccination with F-sKLH shifted the dose-response curves to the right for both fentanyl-induced antinociception and respiratory depression. Naloxone reversed fentanyl effects in both groups, showing that its ability to reverse respiratory depression was preserved. These data demonstrate preclinical selectivity and efficacy of a fentanyl vaccine and suggest that vaccines may offer a therapeutic option in reducing fentanyl-induced side effects.

[A Recombinant Humanized Anticocaine Monoclonal Antibody Alters The Urinary Clearance Of Cocaine And Its Metabolites In Rats](#) Marckel JA, Wetzel HN, Amlal S, Amlal H, Norman AB. Drug Metab. Dispos. 2019; 47(3): 184-188.

A recombinant humanized anticocaine monoclonal antibody, h2E2, has shown potential in the preclinical phases for the treatment of cocaine abuse. The standard tests for cocaine usage are the detection of benzoylecgonine (BE) and cocaine in the urine. This includes workplace drug screens as well as in clinical trials for potential treatments of cocaine abuse. By sequestering cocaine into the plasma compartment, h2E2 prevents cocaine from entering the brain. Due to the altered disposition of cocaine in the presence of h2E2, the authors investigated the effects of h2E2 on cocaine and metabolite levels in the urine of rats to clarify the use of BE as an endpoint measurement for effectiveness in future clinical trials. The urine concentrations of cocaine and metabolites were considerably altered in the presence of h2E2. After a single injection of h2E2 (120 mg/kg) and cocaine hydrochloride (0.56 mg/kg), the concentration of cocaine and BE excreted into the urine of rats decreased by 92% and 91%, respectively, from vehicle controls. Due to the significant decrease in urinary excretion, BE is not an appropriate indicator of cocaine usage in the presence of h2E2. Another endpoint measurement must be selected for the measurement of cocaine usage in the upcoming clinical trials of h2E2. In contrast to the effects on cocaine and BE urinary excretion, there was a 3-fold increase in ecgonine methyl ester (EME) in the presence of h2E2. Therefore, the authors conclude that EME is a more appropriate measurement of cocaine intake in the presence of h2E2.

HIV/AIDS RELATED RESEARCH

[Magnetically Guided Non-Invasive CRISPR-Cas9/gRNA Delivery Across Blood-Brain Barrier To Eradicate Latent HIV-1 Infection](#) Kaushik A, Yndart A, Atluri V, Tiwari S, Tomitaka A, Gupta P, Jayant RD, Alvarez-Carbonell D, Khalili K, Nair M. Sci Rep. 2019 Mar 8; 9(1): 3928. CRISPR-Cas9/gRNA exhibits therapeutic efficacy against latent human immunodeficiency virus (HIV) genome but the delivery of this therapeutic cargo to the brain remains as a challenge. In this research, for the first time, the authors demonstrated magnetically guided non-invasive delivery of a nano-formulation (NF), composed of Cas9/gRNA bound with magneto-electric nanoparticles

(MENPs), across the blood-brain barrier (BBB) to inhibit latent HIV-1 infection in microglia (microglia)/HIV (HC69) cells. An optimized ac-magnetic field of 60 Oe was applied on NF to release Cas9/gRNA from MENPs surface and to facilitate NF cell uptake resulting in intracellular release and inhibition of HIV. The outcomes suggested that developed NF reduced HIV-LTR expression significantly in comparison to unbound Cas9/gRNA in HIV latent microglia/HIV (HC69) cells. These findings were also validated qualitatively using fluorescence microscopy to assess NF efficacy against latent HIV in the microglia cells. The authors believe that CNS delivery of NF (CRISPR/Cas9-gRNA-MENPs) across the BBB certainly will have clinical utility as future personalized nanomedicine to manage neuroHIV/AIDS.

Morphine Counteracts The Antiviral Effect Of Antiretroviral Drugs And Causes Upregulation Of P62/SQSTM1 And Histone-Modifying Enzymes In HIV-Infected Astrocytes

Rodriguez M, Lapierre J, Ojha CR, Pawitwar S, Karuppan MKM, Kashanchi F, El-Hage N. J Neurovirol. 2019 Feb 11. [Epub ahead of print].

Accelerated neurological disorders are increasingly prominent among the HIV-infected population and are likely driven by the toxicity from long-term use of antiretroviral drugs. The authors explored potential side effects of antiretroviral drugs in HIV-infected primary human astrocytes and whether opioid co-exposure exacerbates the response. HIV-infected human astrocytes were exposed to the reverse transcriptase inhibitor, emtricitabine, alone or in combination with two protease inhibitors ritonavir and atazanavir (ERA) with and without morphine co-exposure. The effect of the protease inhibitor, lopinavir, alone or in combination with the protease inhibitor, abacavir, and the integrase inhibitor, raltegravir (LAR), with and without morphine co-exposure was also explored. Exposure with emtricitabine alone or ERA in HIV-infected astrocytes caused a significant decrease in viral replication and attenuated HIV-induced inflammatory molecules, while co-exposure with morphine negated the inhibitory effects of ERA, leading to increased viral replication and inflammatory molecules. Exposure with emtricitabine alone or in combination with morphine caused a significant disruption of mitochondrial membrane integrity. Genetic analysis revealed a significant increase in the expression of p62/SQSTM1 which correlated with an increase in the histone-modifying enzyme, ESCO2, after exposure with ERA alone or in combination with morphine. Furthermore, several histone-modifying enzymes such as CIITA, PRMT8, and HDAC10 were also increased with LAR exposure alone or in combination with morphine. Accumulation of p62/SQSTM1 is indicative of dysfunctional lysosomal fusion. Together with the loss of mitochondrial integrity and epigenetic changes, these effects may lead to enhanced viral titer and inflammatory molecules contributing to the neuropathology associated with HIV.

Cocaine Use And Pre-Exposure Prophylaxis: Adherence, Care Engagement, And Kidney Function

Hojilla JC, Satre DD, Glidden DV, McMahan VM, Gandhi M, Defechereux P, Guanira JV, Mehrotra M, Grant RM, Carrico AW. J Acquir Immune Defic Syndr. 2019 May 1; 81(1): 78-82.

BACKGROUND: Concomitant use of cocaine and HIV pre-exposure prophylaxis (PrEP) raises important clinical questions around adherence, retention in care, and renal toxicity.

METHODS: We assessed the associations of confirmed cocaine use with PrEP adherence (both ascertained through objective measures), care engagement, and renal function in the iPrEx open-label extension. Cocaine use was measured in scalp hair samples and categorized as light (500-3000 pg/mg) and moderate to heavy (>3000 pg/mg). PrEP adherence in the first 3 months was measured through plasma tenofovir concentrations. Disengagement from PrEP care was defined as a gap in follow-up greater than 4 months. Serum creatinine was assessed at baseline and quarterly visits.

RESULTS: Of the 400 participants included in this analysis, 90% were men who have sex with men, 10% transgender women, 74% Hispanic/Latino; 21% tested positive for cocaine use in the last 3 months. In adjusted analysis, light cocaine use [adjusted odds ratio 2.10 (95% confidence interval: 1.07 to 4.14)] and moderate to heavy use [adjusted odds ratio 2.32 (1.08 to 5.00)] were associated with greater odds of having plasma tenofovir concentrations below the level of quantitation. Participants with moderate to heavy use had a nearly 3-fold higher rate of disengagement from PrEP care compared with nonusers (adjusted hazard ratio 2.90 [1.48 to 5.66]). We found no statistically or clinically significant differences in creatinine clearance and serum creatinine between participants who tested positive for cocaine and those who did not.

CONCLUSIONS: Cocaine use decreases PrEP adherence and care engagement. Comprehensive approaches are needed to reduce cocaine use and enhance engagement along the PrEP care continuum.

Differences In The Rate Of Nicotine Metabolism Among Smokers With And Without HIV

Ashare RL, Thompson M, Leone F, Metzger D, Gross R, Mounzer K, Tyndale RF, Lerman C, Mahoney MC, Cinciripini P, George TP, Collman RG, Schnoll R. *AIDS*. 2019 May 1; 33(6): 1083-1088.

OBJECTIVE: HIV-infected smokers lose more life years to tobacco use than to HIV infection. The nicotine metabolite ratio (NMR), a biomarker of CYP2A6, represents individual variation in the rate at which nicotine is metabolized and is associated with response to smoking cessation treatments. We evaluated whether HIV-infected smokers metabolize nicotine faster than HIV-uninfected smokers, which may contribute to the disproportionate smoking burden and may have important treatment implications.

DESIGN: We analysed baseline data from two clinical trials (NCT01710137; NCT01314001) to compare the NMR in HIV-infected smokers (N=131) to HIV-uninfected smokers (N=199).

METHODS: Propensity scores were used to match the groups 2:1 on characteristics that influence NMR: sex, race, BMI and smoking rate. Nicotine metabolites were assessed via liquid chromatography-tandem mass spectrometry methods and the ratio of 3-hydroxycotinine:cotinine was used to compute the NMR.

RESULTS: HIV-infected smokers had significantly higher NMR (mean=0.47, SEM=0.02) and were more likely to be in the highest NMR quartile compared with HIV-uninfected smokers (mean=0.34, SEM=0.02; $P_s < 0.001$).

CONCLUSION: The higher NMR observed among HIV-infected smokers may partially explain higher smoking rates and lower response to transdermal nicotine therapy. Understanding the mechanisms by which HIV and/or ART contribute to faster nicotine metabolism may guide the use of the NMR to personalize tobacco cessation strategies in this underserved population.

Depressive Symptoms At HIV Testing And Two-Year All-Cause Mortality Among Men Who Inject Drugs In Vietnam

Levintow SN, Pence BW, Ha TV, Le MN, Sripaipan T, Latkin CA, Vu PT, Quan VM, Frangakis C, Go VF. *AIDS Behav*. 2019 Mar; 23(3): 609-616.

People who inject drugs (PWID) with HIV experience an elevated risk of death. A potentially important determinant of survival is the high burden of depression. This study examined the relationship of depressive symptoms at HIV testing with 2-year all-cause mortality among newly diagnosed HIV-positive PWID in Vietnam. At HIV testing, 141 PWID (42%) experienced severe depressive symptoms, and over the 2 years following diagnosis, 82 PWID (24%) died. Controlling for potential confounders, the 2-year risk of death among those with depressive symptoms was 9.7% (95% CI - 1.2, 20.6%) higher than the risk among those without depressive symptoms. This

increased risk of mortality for PWID with depressive symptoms was relatively consistent throughout the 2-year period: at 6, 12, and 18 months, the risk difference was 12.6% (5.5-19.7%), 13.9% (4.6-23.2%), and 11.0% (0.9-21.1%), respectively. HIV diagnosis may provide an important opportunity for depression screening and treatment, subsequently improving survival in this key population.

CLINICAL TRIALS NETWORK RESEARCH

Blunts Versus Joints: Cannabis Use Characteristics And Consequences Among Treatment-Seeking Adults

Montgomery L, McClure EA, Tomko RL, Sonne SC, Winhusen T, Terry GE, Grossman JT, Gray KM. Drug Alcohol Depend. 2019 Mar 14; 198: 105-111.

BACKGROUND: Despite the high prevalence of blunt smoking among cannabis users, very few studies examine the clinical profile of blunt smokers relative to those using more common methods of cannabis use, such as joints.

METHODS: The current study uses baseline data from the ACCENT (Achieving Cannabis Cessation-Evaluating N-acetylcysteine Treatment) study, a multi-site randomized pharmacotherapy clinical trial within the National Drug Abuse Treatment Clinical Trials Network, to predict the association between blunt and joint use frequency and cannabis use characteristics (e.g., grams of cannabis used) and consequences (e.g., withdrawal) among past-month cannabis users (N = 377) who were screened for study participation.

RESULTS: After controlling for race, age, gender, other forms of cannabis use (including joint use) and nicotine dependence, multivariable linear regression models indicated that the number of days of blunt use in the past month was a significant predictor of the average amount of cannabis per using day ($t = 3.04$, $p < .01$), the estimated average cost of cannabis ($t = 2.28$, $p < .05$) and Cannabis Withdrawal Scale scores ($t = 1.94$, $p < .05$). Frequency of joint use did not significantly predict any of the cannabis use characteristics or consequences.

CONCLUSIONS: Blunt smokers may present to treatment with greater amounts of cannabis smoked and more intense withdrawal symptoms, which may adversely impact their likelihood of successful abstinence. Cannabis-dependent blunt smokers may be more likely to benefit from treatment that targets physiological and mood-related withdrawal symptoms.

Medical Complications Associated With Substance Use Disorders In Patients With Type 2 Diabetes and Hypertension: Electronic Health Record Findings

Winhusen T, Theobald J, Kaelber DC, Lewis D. Addiction. 2019 Mar 9. [Epub ahead of print].

BACKGROUND AND AIMS: Screening for substance use disorder (SUD) in general medical settings may be particularly important in patients with comorbid health conditions exacerbated by SUD. This study evaluated whether SUD is associated with type 2 diabetes mellitus (T2DM) complications in patients with co-occurring T2DM and hypertension.

DESIGN: Analysis of a limited data set obtained through IBM Watson Health Explorays, a platform integrating data from electronic health records. Matched controls were defined for each of five SUDs: tobacco use disorder (TUD), opioid use disorder (OUD), cocaine use disorder, cannabis use disorder (CUD) and alcohol use disorder (AUD) using Mahalanobis distance within propensity score calipers.

SETTING: All patients were seen in the MetroHealth System (Cleveland, OH, USA) and had diagnosis codes for T2DM and hypertension.

PARTICIPANTS: SUD group participants had a diagnosis of abuse/dependence for the substance of interest. Controls for each SUD group had no diagnosis code related to the SUD of interest and

were selected to match the SUD patients on demographics, residential zip code median income and body mass index. Total sample sizes for each SUD-control comparison ranged from 1160 for CUD to 22 128 for TUD.

MEASUREMENTS: Outcome was diagnosis (yes/no) of four T2DM complications (cerebrovascular accident, diabetic neuropathy, diabetic renal disease, myocardial infarction) and all-cause mortality.

FINDINGS: Logistic regressions revealed that SUD was significantly associated with greater risk of cerebrovascular accident [TUD odds ratio (OR) = 1.79, OUD-OR = 1.94, cocaine use disorder OR = 2.67], diabetic neuropathy [TUD-adjusted OR (aOR) = 1.47, cocaine use disorder-aOR = 1.35, AUD-aOR = 1.27], diabetic renal disease (TUD-aOR = 1.25, OUD-OR = 1.34), myocardial infarction (TUD-OR = 1.96, OUD-OR = 2.01, cocaine use disorder-OR = 2.68, CUD-OR = 2.48, AUD-OR = 1.42) and mortality (TUD-OR = 1.15, cocaine use disorder-OR = 1.61, CUD-OR = 1.49, AUD-OR = 1.35).

CONCLUSIONS: Among patients in Ohio USA with both type 2 diabetes mellitus (T2DM) and hypertension, those with substance use disorders appear to have greater risk for T2DM complications and all-cause mortality.

[Relationship Between Tobacco Use And Health-Related Quality Of Life \(HRQoL\) Among Clients In Substance Use Disorders Treatment](#) Campbell B, Yip D, Le T, Gubner N, Guydish J. J Psychoactive Drugs. 2019 Jan-Mar; 51(1): 48-57. Epub 2018 Dec 20.

The authors examined relationships of smoking status and tobacco-related variables with health-related quality of life (HRQoL), a metric of disease burden, among clients in substance use disorders (SUDs) treatment. Participants (N = 2,068; 46.6% female) completed surveys reporting demographics, smoking status, and past-month days they experienced physical and/or mental health distress. Smokers (n = 1,596; 77.2% of sample) answered questions on tobacco-related variables. Multinomial regression models assessed relationships between tobacco-related variables (smoking status, nicotine dependence, menthol smoking, electronic-cigarette use, health concerns, and cost as reasons affecting reducing/quitting smoking, past and future quit attempts) with HRQoL in four categories (good health, physical health distress, mental health distress, or both physical and mental health distress). Current smokers were more likely than former smokers to report frequent physical and mental health distress than good health (OR = 1.97, 95% CI = 1.16, 3.34), as were smokers with higher nicotine dependence (OR = 1.18, 95% CI = 1.03, 1.35). Smokers reporting both frequent physical and mental health distress were more sensitive to cigarettes' cost (OR = 1.56, 95% CI = 1.06, 2.29), and less likely to use e-cigarettes (OR = 0.59, 95% CI = 0.38, 0.94). Findings of poor HRQoL among nicotine-dependent smokers with additional SUDs strengthen the imperative to provide smoking cessation interventions in addictions treatment.

[Prevalence Of Obesity For Opioid- And Stimulant-Dependent Participants In Substance Use Treatment Clinical Trials](#) Hu L, Matthews A, Shmueli-Blumberg D, Killeen TK, Tai B, VanVeldhuisen P. Drug Alcohol Depend. 2018 Sep 1; 190: 255-262. Epub 2018 Jul 20.

AIMS: To estimate obesity prevalence among drug-dependent individuals and to compare prevalence across different types of drug dependence.

METHODS: 1596 opioid- and/or stimulant-dependent participants were extracted from six clinical trials within the National Drug Abuse Treatment Clinical Trials Network of the National Institute on Drug Abuse (NIDA CTN) to estimate obesity prevalence among drug-dependent users. Age-, sex-, and race-matched National Health and Nutrition Examination Survey (NHANES) samples were used as a general population reference. Standardized prevalence ratios (SPRs) were calculated

to compare the CTN sample to NHANES as well as to compare within the CTN sample. Logistic regression estimated associations between the type of drug dependence and obesity.

RESULTS: The standardized obesity prevalence among the drug-dependent CTN trial participants was 67% of expected for age-, sex- and race-matched NHANES participants (SPR = 0.67, 95% CI: 0.60-0.74). Obesity was least prevalent among opioid-dependent-only participants (SPR = 0.36, 95% CI: 0.27-0.46 compared to the NHANES, and SPR = 0.33, 95% CI: 0.23-0.46 compared to the stimulant-dependent-only participants). Compared to stimulant-dependent-only users ($p < 0.0001$), the odds of obesity were 67% lower among opioid-dependent-only users (adjusted odds ratio [AOR] = 0.33, 95% CI: 0.23-0.46) and 33% lower among opioid and stimulant-co-dependent users (AOR = 0.67, 95% CI: 0.49-0.90) after controlling for age, sex, race, education and employment pattern.

CONCLUSIONS: The prevalence of obesity among drug-dependent clinical trial participants was lower than the general population, and lowest among opioid-dependent-only users, suggesting an inverse relationship between obesity prevalence and drug dependence, most notable among opioid-dependent-only users.

ADOLESCENT BRAIN COGNITIVE DEVELOPMENT STUDY RESEARCH

[Association Of Prenatal Cannabis Exposure With Psychosis Proneness Among Children In The Adolescent Brain Cognitive Development \(ABCD\) Study](#) Fine JD, Moreau AL, Karcher NR, Agrawal A, Rogers CE, Barch DM, Bogdan R. JAMA Psychiatry. 2019 Mar 27. [Epub ahead of print].

Cannabis use during adolescence has been linked to triggering or worsening symptoms of psychosis, but little is known about the effects of prenatal exposure on future psychosis proneness in the children. Considering the 75% increase in past-month marijuana use among pregnant mothers in the United States from 2002 to 2016, understanding the impact of prenatal exposure on children is critical. This study examines the association between prenatal cannabis exposure, both before and after maternal awareness of pregnancy, on the proneness to psychosis in ABCD study participants. The authors examined self-reported psychotic-like experiences from the prodromal questionnaire-brief child version using linear mixed-effects models on data from the 1.0 data release, which included 4361 children aged 9-10 years of which 201 were prenatally exposed to marijuana. Of those, 138 were exposed only before maternal knowledge of pregnancy, 61 were exposed before and after maternal knowledge of pregnancy, and 2 were exposed only after maternal knowledge of pregnancy. Marijuana use after knowledge of pregnancy was associated with small increases in offspring psychosis proneness even when controlling for potentially confounding variables (i.e. child-, mother- and pregnancy-related variables) or variables significantly associated with psychosis proneness (i.e., maternal education, unplanned pregnancy, family history of psychosis, female child, cannabis use after knowledge of pregnancy, and if the child had ever tried a sip of alcohol or puff of tobacco). Marijuana use before maternal knowledge of pregnancy was associated with increased psychosis proneness only in models without these fixed-effect covariates. These findings indicate that cannabis exposure after, but not before, maternal knowledge of pregnancy may result in an increased risk of psychosis proneness in offspring, before those children have initiated marijuana use themselves. This study could have important implications regarding the safety of cannabis usage during pregnancy.

INTRAMURAL RESEARCH

Medicinal Chemistry Section Molecular Targets and Medications Discovery Branch

Translating The Atypical Dopamine Uptake Inhibitor Hypothesis Toward Therapeutics For Treatment Of Psychostimulant Use Disorders

Newman AH, Cao J, Keighron JD, Jordan CJ, Bi GH, Liang Y, Abramyan AM, Avelar AJ, Tschumi CW, Beckstead MJ, Shi L, Tanda G, Xi ZX. *Neuropsychopharmacology*. 2019 March 11. [Epub ahead of print].

Medication-assisted treatments are unavailable to patients with cocaine use disorders. Efforts to develop potential pharmacotherapies have led to the identification of a promising lead molecule, JJC8-091, that demonstrates a novel binding mode at the dopamine transporter (DAT). Here, JJC8-091 and a structural analogue, JJC8-088, were extensively and comparatively assessed to elucidate neurochemical correlates to their divergent behavioral profiles. Despite sharing significant structural similarity, JJC8-088 was more cocaine-like, increasing extracellular DA concentrations in the nucleus accumbens shell (NAS) efficaciously and more potently than JJC8-091. In contrast, JJC8-091 was not self-administered and was effective in blocking cocaine-induced reinstatement to drug seeking. Electrophysiology experiments confirmed that JJC8-091 was more effective than JJC8-088 at inhibiting cocaine-mediated enhancement of DA neurotransmission. Further, when VTA DA neurons in DAT-cre mice were optically stimulated, JJC8-088 produced a significant leftward shift in the stimulation-response curve, similar to cocaine, while JJC8-091 shifted the curve downward, suggesting attenuation of DA-mediated brain reward. Computational models predicted that JJC8-088 binds in an outward facing conformation of DAT, similar to cocaine. Conversely, JJC8-091 steers DAT towards a more occluded conformation. Collectively, these data reveal the underlying molecular mechanism at DAT that may be leveraged to rationally optimize leads for the treatment of cocaine use disorders, with JJC8-091 representing a compelling candidate for development.

Behavioral Neurophysiology Research Section Cellular Neurobiology Research Branch

Expectancy-Related Changes In Dopaminergic Error Signals Are Impaired By Cocaine Self-Administration

Takahashi YK, Stalnaker TA, Marrero-Garcia Y, Rada RM, Schoenbaum G. *Neuron*. 2019 Jan 16; 101(2): 294-306.

Addiction is a disorder of behavioral control and learning. While this may reflect pre-existing propensities, drug use also clearly contributes by causing changes in outcome processing in prefrontal and striatal regions. This altered processing is associated with behavioral deficits, including changes in learning. These areas provide critical input to midbrain dopamine neurons regarding expected outcomes, suggesting that effects on learning may result from changes in dopaminergic error signaling. Here, the authors show that dopamine neurons recorded in rats that had self-administered cocaine failed to suppress firing on omission of an expected reward and exhibited lower amplitude and imprecisely timed increases in firing to an unexpected reward. Learning also appeared to have less of an effect on reward-evoked and cue-evoked firing in the cocaine-experienced rats. Overall, the changes are consistent with reduced fidelity of input regarding the expected outcomes, such as their size, timing, and overall value, because of cocaine.

**Biobehavioral Imaging and Molecular Neuropsychopharmacology Section
Neuroimaging Research Branch**

[Ultrapotent Chemogenetics For Research and Potential Clinical Applications](#) Magnus CJ, Lee PH, Bonaventura J, Zemla R, Gomez JL, Ramirez M, Hu X, Galvan A, Basu J, Michaelides M, Sternson SM. Science. 2019 Mar 14. pii: eaav5282. [Epub ahead of print].

Chemogenetics enables non-invasive chemical control over cell populations in behaving animals. However, existing small molecule agonists show insufficient potency or selectivity. There is also need for chemogenetic systems compatible with both research and human therapeutic applications. The authors developed a new ion channel-based platform for cell activation and silencing that is controlled by low doses of the anti-smoking drug varenicline. They then synthesized novel sub-nanomolar potency agonists, called uPSEMs, with high selectivity for the chemogenetic receptors. uPSEMs and their receptors were characterized in brains of mice and a rhesus monkey by in vivo electrophysiology, calcium imaging, positron emission tomography, behavioral efficacy testing, and receptor counterscreening. This platform of receptors and selective ultrapotent agonists enables potential research and clinical applications of chemogenetics.

**Integrative Neurobiology Section
Molecular Targets and Medications Discovery Branch**

[Opioid-Galanin Receptor Heteromers Mediate The Dopaminergic Effects Of Opioids](#)

Cai NS, Quiroz C, Bonaventura J, Bonifazi A, Cole TO, Purks J, Billing AS, Massey E, Wagner M, Wish ED, Guitart X, Rea W, Lam S, Moreno E, Casadó-Anguera V, Greenblatt AD, Jacobson AE, Rice KC, Casadó V, Newman AH, Winkelman JW, Michaelides M, Weintraub E, Volkow ND, Belcher AM, Ferré S. J Clin Invest. 2019 Mar 26;130.

Identifying non-addictive opioid medications is a high priority in medical sciences, but μ -opioid receptors mediate both the analgesic and addictive effects of opioids. The authors found a significant pharmacodynamic difference between morphine and methadone that is determined entirely by heteromerization of μ -opioid receptors with galanin Gal1 receptors, rendering a profound decrease in the potency of methadone. This was explained by methadone's weaker proficiency to activate the dopaminergic system as compared to morphine and predicted a dissociation of therapeutic versus euphoric effects of methadone, which was corroborated by a significantly lower incidence of self-report of "high" in methadone-maintained patients. These results suggest that μ -opioid-Gal1 receptor heteromers mediate the dopaminergic effects of opioids, which may lead to a lower addictive liability of opioids with selective low potency for the μ -opioid-Gal1 receptor heteromer, exemplified by methadone.

Magnetic Resonance Imaging and Spectroscopy Section Neuroimaging Research Branch

[Compulsive Drug Use Is Associated With Imbalance Of Orbitofrontal- And Prelimbic-Striatal Circuits In Punishment-Resistant Individuals](#)

Hu Y, Salmeron BJ, Krasnova IN, Gu H, Lu H, Bonci A, Cadet JL, Stein EA, Yang Y. Proc Natl Acad Sci U S A. 2019 Apr 15. pii: 201819978. [Epub ahead of print].

Substance use disorders (SUDs) impose severe negative impacts upon individuals, their families, and society. Clinical studies demonstrate that some chronic stimulant users are able to curtail their drug use when faced with adverse consequences while others continue to compulsively use drugs. The mechanisms underlying this dichotomy are poorly understood, which hampers the development of effective individualized treatments of a disorder that currently has no FDA approved pharmacological treatments. In the present study, using a rat model of methamphetamine self-administration (SA) in the presence of concomitant foot shocks, thought to parallel compulsive drug taking by humans, we found that SA behavior correlated with alterations in the balance between an increased orbitofrontal cortex-dorsomedial striatal “go” circuit and a decreased prelimbic cortex-ventrolateral striatal “stop” circuit. Critically, this correlation was seen only in rats who continued to self-administer at a relatively high rate despite receiving foot shocks of increasing intensity. While the “stop” circuit functional connectivity became negative after repeated SA in all rats, “shock resistant” rats showed strengthening of this negative connectivity after shock exposure. In contrast, “shock sensitive” rats showed a return towards their baseline levels after shock exposure. These results may help guide novel non-invasive brain stimulation therapies aimed at restoring the physiological balance between “stop” and “go” circuits in SUDs.

Neurocircuitry of Motivation Section Behavioral Neuroscience Research Branch

[Incubation Of Cocaine Craving After Intermittent Access Cocaine Self-Administration: Sex Differences and Estrous Cycle](#)

Nicolas C, Russell TI, Pierce AF, Maldera S, Holley A, You ZB, McCarthy MM, Shaham Y, Ikemoto S. Biol Psychiatry. 2019 Jan 29. pii: S0006-3223(19)30042-3. [Epub ahead of print].

BACKGROUND: Studies using continuous-access drug self-administration showed that cocaine seeking increases during abstinence (incubation of cocaine craving). Recently, studies using intermittent-access self-administration showed increased motivation to self-administer and seek cocaine. We examined whether intermittent cocaine self-administration would potentiate incubation of craving in male and female rats and examined the estrous cycle's role in this incubation.

METHODS: In experiment 1, male and female rats self-administered cocaine either continuously (8 hours/day) or intermittently (5 minutes ON, 25 minutes OFF × 16) for 12 days, followed by relapse tests after 2 or 29 days. In experiments 2 and 3, female rats self-administered cocaine intermittently for six, 12, or 18 sessions. In experiment 4, female rats self-administered cocaine continuously followed by relapse tests after 2 or 29 days. In experiments 3 and 4, the estrous cycle was measured using a vaginal smear test.

RESULTS: Incubation of cocaine craving was observed in both sexes after either intermittent or continuous drug self-administration. Independent of access condition and abstinence day, cocaine seeking was higher in female rats than in male rats. In both sexes, cocaine seeking on both abstinence days was higher after intermittent drug access than after continuous drug access. In

female rats, incubation of craving after either intermittent or continuous drug access was significantly higher during estrus than during non-estrus; for intermittent drug access, this effect was independent of the training duration.

CONCLUSIONS: In both sexes, intermittent cocaine access caused time-independent increases in drug seeking during abstinence. In female rats, the time-dependent increase in drug seeking (incubation) is critically dependent on the estrous cycle phase.

GRANTEE HONORS AND AWARDS

Margaret Gnegy, Ph.D., a Professor in the Department of Pharmacology and Associate Chair of Education was elected to AAAS Fellow, section on Neuroscience.

Andrea G. Hohmann, Ph.D., a Professor in the Department of Psychological and Brain Sciences and the Linda and Jack Gill Chair of Neuroscience at Indiana University, was elected to AAAS Fellow, section on Neuroscience.

Caryn Lerman, Ph.D., who recently became the Director of the Norris Comprehensive Cancer Center at the University of Southern California, was honored with the Ferno Clinical Research Award by the Society for Research on Nicotine and Tobacco at its annual meeting.

STAFF HONORS AND AWARDS

STAFF HONORS

Rao Rapaka, Ph.D., Division of Neuroscience and Behavior, was honored with a Lifetime Achievement Award from the Society on Neuroimmune Pharmacology at its annual meeting held April 2019 in Portland, OR.

Rao Rapaka, Ph.D., was honored with a Lifetime Achievement Award from the University of Arizona at its Symposium on Pain and Addiction, held in Tucson, AZ, in April 2019.

Roger Sorenson, Ph.D., Division of Neuroscience and Behavior, was honored with an Outstanding Service Award from the Society on Neuroimmune Pharmacology at its annual meeting held April 2019 in Portland, OR.

David Thomas, Ph.D., Division of Epidemiology, Services and Prevention Research, received the 2019 American Pain Society John and Emma Bonica Public Service Award honoring outstanding contributions by an individual or an organization to the field of pain through public education, dissemination of information, public service, or other efforts to further knowledge about pain. The award is named for John Bonica, a leading force in the development of the pain treatment movement, and his wife, Emma.

STAFF CHANGES

Mehdi Farokhnia, M.D., has been appointed as a Research Fellow in Dr. Leggio's NIDA/NIAAA Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN). Before that, he was a Post-Doc Fellow in the CPN Section. Dr. Farokhnia has conducted several projects, including two major clinical protocols as Lead Associate Investigator. He is also interested in investigating innovative methodological approaches that may best translate preclinical findings into human research, with a focus on behavioral pharmacology and substance use.

New Staff

Gillian Acca, Ph.D., joined NIDA in February as a Health Science Policy Analyst working on all activities related to the NIDA Advisory Council as well as programs and initiatives in the Office of Research Training. She joins NIDA from the NIH Office of the Director's Office of Behavioral and Social Sciences Research.

Jennifer Cho joined the Division of Extramural Research as a Grants Management Specialist in February 2019. Jennifer earned a B.A. and B.M. in English Literature and Opera Performance from Northwestern University. She worked as a Program Coordinator in the Department of Applied Math and DEES at Columbia University from July 2002 through January 2010, working on planning, implementation and evaluations of grants, cost-share agreements, and agency agreements. In August 2010, she joined NIH as a Grants Management Specialist. Over the past 8 years, she has worked at three different Institutes coordinating a variety of grant programs, independently managing a portfolio of networks, domestic and foreign grants with complex award mechanisms and multimillion-dollar budgets.

Holly Moore, Ph.D., joined the Division of Neuroscience and Behavior as a Program Officer. She has a Ph.D. in Neuroscience from Ohio State University and did postdoctoral research at the University of Pittsburgh, where she studied the function of prefrontal cortico-basal ganglia circuits. She went on to become a faculty member in the Department of Psychiatry at Columbia, where she led systems and behavioral neuroscience research to understand the basis of neuropsychiatric disease, and was part of translational research programs as well. Her knowledge and expertise will be invaluable to the goals of the branch and division.

Jennifer Wenzel, Ph.D., joined NIDA to help launch the Common Fund Acute to Chronic Pain Signatures Program. She will also serve as a Program Officer in the Behavioral Cognitive Neuroscience Branch of the Division of Neuroscience and Behavior. Dr. Wenzel holds a Ph.D. in Neuroscience and Behavior from UC Santa Barbara. She conducted postdoctoral research at the University of Maryland School of Medicine. Dr. Wenzel's areas of expertise include behavioral pharmacology, rodent models of reward, aversion, and reinforcement, opto- and chemo-genetic dissection of motivational brain circuits, and the use of fast scan cyclic voltammetry and fiber photometry to measure neurochemical activity.

Julia Zur, Ph.D., joined the Division of Epidemiology, Services and Prevention Research's Services Research Branch as the Program Official for the Justice Community Opioid Innovation

Network. Most recently, Dr. Zur worked at the Kaiser Family Foundation, where she focused her work on understanding Medicaid's role in addressing the opioid epidemic.

Leonardo Angelone, Ph.D., joined the Office of Translational Initiatives and Program Innovations in the Office of the Director as a Health Science Administrator in March 2019. Dr. Angelone's areas of responsibility will include Small Business Innovation Research/Small Business Technology Transfer Programs and FDA-regulated Medical Devices. Dr. Angelone comes to NIDA from a position with the FDA.

Ram Arudchandran, Ph.D., joined the Office of Translational Initiatives and Program Innovations in the Office of the Director as a Health Science Administrator in March 2019. His areas of responsibility will include Small Business Innovation Research/Small Business Technology Transfer Programs and therapeutics and biomarker development and validation. Dr. Arudchandran comes to NIDA from a position with the U.S. Army Medical Research and Materiel Command.

Alexander Beraud joined the Office of Management's Office of Acquisition as a Contract Specialist on February 3, 2019. Mr. Beraud comes to NIDA from a position in the private sector.

Eva Bouzis joined the Office of Management's Office of Acquisition as a Contract Specialist on March 3, 2019. Ms. Bouzis comes to NIDA from a position with National Heart, Lung, and Blood Institute.

Minki Chitterji, Ph.D., joined the Division of Epidemiology, Services and Prevention Research's Prevention Research Branch as a Health Scientist Administrator on February 17, 2019. Dr. Chitterji comes to NIDA from a position with the National Institute on Child Health and Human Development.

Thien Nguyen joined the Office of Management's Office of Acquisition as a Contract Specialist on March 3, 2019. Mr. Nguyen comes to NIDA from a position with the Department of Health and Human Services Program Support Center.

Renu Simon joined the Office of Management's Office of Acquisition as a Contract Specialist on February 3, 2019. Mr. Simon comes to NIDA from a position with the National Heart, Lung, and Blood Institute.

Staff Departures

Julia Berzhanskaya, Ph.D., who emphasized small business, neuromodulation, devices and contract reviews while in the NIDA Division of Extramural Research/Office of Extramural Policy and Review/Scientific Review Branch, has left NIDA to assume a Program Officer position within the NIH Office of the Director's Division of Construction and Instruments.

Jessica Hemmati, an Ethics Coordinator in the Office of Management's Office of the Director, left NIDA on March 30, 2019, for a position in the NIH Office of the Director.

Jinhee Lee, Pharm.D., Captain PHSCC, Deputy Chief of the Public Information and Liaison Branch, Office of Science Policy and Communications, transferred to the U.S. Food and Drug Administration in March 2019.

Megan Nathan, a Contract Specialist in the Office of Management's Office of Acquisitions, left NIDA on March 16, 2019, for a position with the U.S. Department of Education.

David Thomas, Ph.D., Division of Epidemiology, Services and Prevention Research, left NIDA for a position as Senior Advisor to the Director of the Office of Research on Women's Health.

Christopher Weaver, a Contract Specialist in the Office of Management's Office of Acquisitions, left NIDA on February 16, 2019, for a position with NIAID.

Retirements

Genevieve deAlmeida Morris, Ph.D., Health Research Evaluator, Science Policy Branch, Office of Science Policy and Communications, retired in February 2019.

Carol Krause, Chief of the Public Information and Liaison Branch, Office of Science Policy and Communications, retired in March 2019 after 13 years of federal service.

In Memoriam

We are saddened by the loss of a cherished colleague of the NIDA community, **Gavril W. Pasternak, M.D., Ph.D.**, who passed away on February 22, 2019. Dr. Pasternak was an internationally recognized scientist from Memorial Sloan Kettering Cancer Center whose research helped to shape current knowledge of opioid receptors and pharmacology. He is also recognized for his mentorship and nurturing the careers of many successful neuropharmacologists and neuroscientists. He was also known as a devoted patient advocate. He will be genuinely missed.



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